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Editorial Review

What Did We Learn about VADs in 2019?

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Introduction

This is our 6th annual literature review on mechanical circulatory support (MCS) devices.

Our previous reports for [2014](#), [2015](#), [2016](#), [2017](#), [2018](#) were published as open access articles and were well received by the readers (1-5). In this paper, we summarize the most interesting and important, from our standpoint, publications from 2019. As we have done for the past two years, a section on extracorporeal membrane oxygenation (ECMO) is included and primarily addresses new developments in veno-arterial ECMO (VA ECMO) use.

Readers who wish to supplement this review, to argue with the author's statements or to express their opinions are encouraged to do so by sending letters to the editor mguglin@iu.edu or posting on our Facebook page at <https://www.facebook.com/TheVADJournal>.

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Outcomes

The outcomes for patients on left ventricular assist device (LVAD) support remains much the same when compared to 2018. The 2019 annual report from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) confirmed an ongoing shift in the use of LVAD for less acute (profile 3) patients (1). One-year survival on continuous flow devices was 83%, and 5-year survival was 46%. The one-year survival rates for centrifugal-flow and axial-flow devices were 85% and 84%, respectively. At one year, stroke occurred in 20% of patients on centrifugal-flow support and 13% of patients on axial-flow support ($p < 0.001$); gastrointestinal bleeding (GIB) affected 20% and 25% ($p < 0.001$); and pump-related infections occurred in 28% and 25% of patients, respectively ($p = 0.01$). Neurologic dysfunction (19% of deaths) and multisystem organ dysfunction (15%) were the most common causes of death (1).

Device Studies

HeartMate II vs. HeartMate 3

The final analysis from the Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate® 3 (HM3, MOMENTUM 3, Abbott), a randomized trial comparing the HM3 and HeartMate II (HMII), was published last year (2). Patients were randomly assigned to receive either the centrifugal-flow (HM3) or the axial-flow pump (HMII) irrespective of the intended goal of use (bridge to transplantation or destination therapy). At two years post-implantation, 76.9% in the HM3 group, as compared with 64.8% in the HMII group, remained alive and free of disabling stroke or reoperation to replace or remove a malfunctioning device, which was the primary endpoint of the trial (relative risk, 0.84; 95% confidence interval [CI], 0.78-0.91; $P < 0.001$ for superiority). Pump replacement at two years, the secondary endpoint, was less common in the centrifugal-flow pump group than in the axial-flow pump group (2.3% vs. 11.3%; relative risk, 0.21; 95% CI, 0.11-0.38; $P < 0.001$). The numbers of events per patient-year for a stroke of any severity, major bleeding, and gastrointestinal hemorrhage were lower in the centrifugal-flow pump group than in the axial-flow pump group. There was no significant difference in overall survival between the groups (2).

A substudy of the same trial compared strokes in patients supported with these two pumps and found that the HM3 pump was associated with a marked reduction in stroke rates compared with the HMII (3). Although there was no short-term difference in stroke rate (up to 180 days), stroke incidence in the long-term period (181-730 days after LVAD) was 3.3 times lower for the HM3 group (HM3: 0.04 versus HMII: 0.13 events per patient-year; odds ratio, 0.23; 95% CI, 0.08-0.63; $P = 0.01$). There was no direct association of blood pressure (BP) or antithrombotic regimens with observed stroke rates. A stroke significantly lowered 2-year survival: 43 ± 12% for hemorrhagic stroke, 57 ± 9% for ischemic stroke, 51 ± 11% for disabling, and 51 ± 11% for nondisabling compared with 85 ± 2% 2-year survival for patients without stroke (3).

Importantly, as compared to other continuous-flow pumps, the HM3 is likely related to lower shear stress due to its fully magnetically levitated rotor. It is well known



that von Willebrand factor (vWF) and acquired von Willebrand syndrome play a major role in the origin of GIB complications in patients with continuous-flow LVADs. In a study published from the Continued Access Protocol of the MOMENTUM3 trial, the high molecular weight multimers of vWF were better preserved in the HM3 than in HMII supported patients (4). Also, patients with HM3 devices had a higher level of vWF activity during device support, which may reduce the formation of arteriovenous malformations and lead to a lower bleeding complication rate (5).

Fully-Implantable LVAD

There is a consensus in the MCS world that eliminating the driveline and all associated problems would be a breakthrough leading to a dramatically improved quality of life for patients with LVADs. A fully implantable LVAD option would increase the appeal of this intervention to patients, families, and physicians. Last year, two human patients received fully-implantable LVADs (LeviticusCardio, Ltd., Petach Tikva, Israel) in Astana, Kazakhstan (6). The system was integrated with the Jarvik 2000 (Jarvik Heart, Inc.) and consists of an internal integrated controller and battery coupled with an internal thoracic coil ring designed for energy harvesting. The required energy was delivered to the device via a coplanar energy transfer system comprised of two large rings utilizing a coil-within-the-coil topology. This system ensures robust resonance energy transfer while allowing for substantial (>6 hours) unholstered circulatory support powered by an implantable battery source. The external equipment includes a power transmission belt coupled with an external controller, battery, and wristwatch monitor. One patient had early pump thrombosis and a perioperative stroke with a major residual deficit. The second patient reached full ambulation, including swimming, within the first week of surgery, was discharged from the hospital, and successfully transplanted thereafter (6).

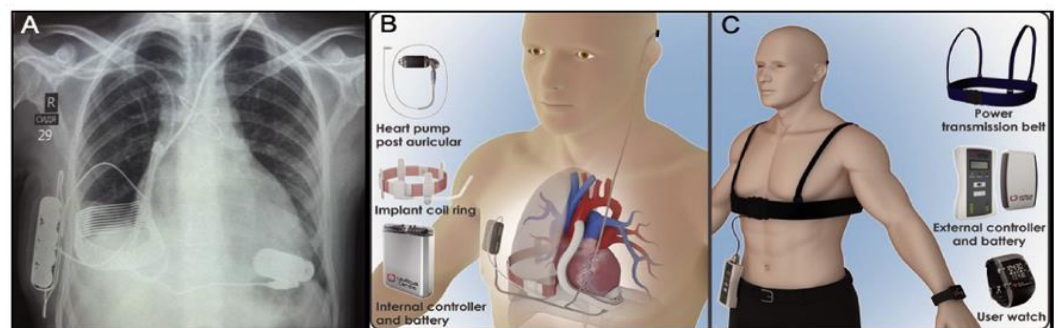


Figure 1. A. Chest X-ray depicting implantable components topography, B. Implantable components C. External components. Reproduced from Pya et al. (6), with permission



Candidate Selection

Most programs do not have a rigid upper age limit for LVAD candidates. Nevertheless, it is important to remember that elderly patients are at a survival disadvantage. A majority (84.5%) of younger patients (< 55 years old) are discharged to home, but only 46.8% of adults over 75 years of age were discharged home following implantation ($p < 0.001$) (7). Post-implantation survival was 69.6%, 46.2%, and 31.7% at 1-, 3-, and 5-years in patients older than 75 years of age, respectively, which is starkly different than the respective survival rates (87.7%, 70.3%, and 53.7%) of patients less than 55 years of age ($p < 0.001$) (7).

Also, elderly patients with LVADs had a higher incidence of GIB but lower rates of device thrombosis (adjusted hazard ratio [HR] for GIB: 2.52; 95% CI, 2.24-2.84) compared to those younger than 55 years of age (7). On the other hand, the hazard ratios of pump thrombosis were lower in the oldest cohort (adjusted HR, 0.40; 95% CI, 0.31-0.52), which might justify a lower intensity of anticoagulation in this population (7).

Pulmonary vascular resistance (PVR), calculated as a transpulmonary gradient (mean pulmonary artery pressure minus pulmonary capillary wedge pressure) divided by cardiac output, is routinely calculated during transplant/LVAD evaluation. According to Uriel et al. (8), the transpulmonary gradient, which is directly measured, rather than calculated, and therefore is less susceptible to error, is more valid for prognosis. However, the transpulmonary gradient scores did not predict survival while on LVAD support. In patients who were successfully transplanted after being bridged with LVAD, a transpulmonary gradient of >10 mm Hg, which was the median on pre-LVAD measurement, was associated with reduced one-year survival rates (80% vs. 91%; $p = 0.016$). To the contrary, below or above the median PVR pre-LVAD did not impact survival rates (8).

The pulmonary function study, which is another routine test during candidate selection, does not appear useful. There was no association between baseline pulmonary function tests and survival time post-LVAD or the incidence of perioperative right ventricular (RV) failure (9).

Another study looked into candidates who were referred for LVAD evaluation and were rejected by the selection committee at a single center (10). Their yearly acceptance rate ranged between 57% and 75%. Reasons for rejection included: patient being too sick (34%); psychosocial concerns (25%); patient declined (16%); decision was deferred for medical optimization (15%); or patient being too healthy (10%). Psychosocial concerns included poor social support (71%), a history of non-compliance (16%), and a history of drug abuse (13%) (10). The one-year survival of rejected patients was 42% in those who were too sick, 64% in those with psychosocial concerns, 68% in patients who declined, 86% in those deferred for medical optimization, and 100% in those too healthy ($P < 0.01$). A subset analysis of 40 patients who were rejected because of poor social support had a 46% one-year mortality (10). These data may be a sign that increasing flexibility in patient acceptance by the programs may be beneficial for the patients. Denial of a life-saving device because of circumstances that the patient cannot control sentences them to a 50% chance of death in the next year. While we all



want our patients with LVADs to be safe, the rate of life-threatening situations on LVAD support is certainly less than 50% a year.

Management of Patients on LVAD Support

Multidisciplinary team

Last year, the Montefiore LVAD program implemented a number of changes in their protocols that were associated with a significant increase in one-year survival (74.6% to 100% [$p=0.0002$]) (11). Further, one-year survival free of serious adverse events (reoperation to replacement of the device or disabling stroke) increased from 70.4% to 84.9% ($p=0.059$). At the same time, rates for disabling stroke, measured as event per patient-year, decreased from 0.15 to 0, ($p=0.019$). Rates of GIB decreased from 0.87 to 0.51 ($p=0.11$) as did driveline infection rates (0.24 to 0.10, $p=0.18$). The changes included:

- daily, simultaneous cardiology/cardiac surgery/critical care/pharmacy/coordinator rounds
- pharmacist-directed anticoagulation
- speed optimization echocardiogram before discharge
- comprehensive device thrombosis screening and early intervention
- use of a BP clinic with pulsatility-adjusted goals
- early follow-up after discharge
- individual long-term coordinator/cardiologist assignment
- systematic training and credentialing of ancillary in-hospital providers (11).

Emergencies on LVAD

The Heart Failure Society of America, the Society for Academic Emergency Medicine, and the International Society for Heart and Lung Transplantation published an expert consensus document that included a decision matrix to guide the management of emergencies in LVAD patients (12).

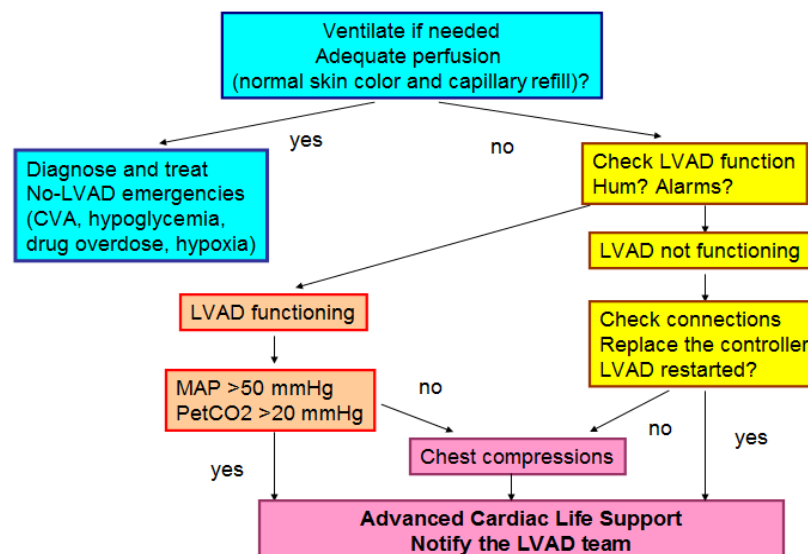


Figure 2. Modified flowchart from Givertz et al. (12).



For comparison, we are reproducing our own algorithm published in the *VAD Journal* (13).

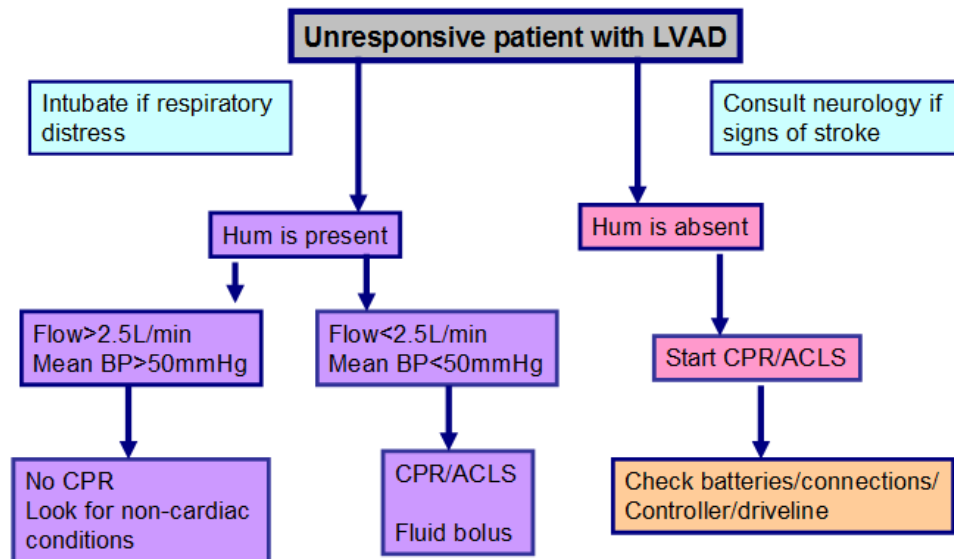


Figure 3. Approach to Unresponsive patient with LVAD (13)

Optimization of Blood Pressure

The discussion regarding optimal BP and BP control in patients with LVADs is ongoing. According to a study of INTERMACS data, patients with chronically low mean arterial pressure (MAP, ≤ 75 mm Hg), Doppler (≤ 80 mm Hg), and systolic BP (< 90 mm Hg) had a 35%-42% higher adjusted HR of death as compared to patients with a normal or high BP ($p \leq 0.0001$) (14). At the same time, patients with higher than normal BP (MAP > 100 mm Hg, Doppler ≥ 105 mm Hg, and systolic BP ≥ 120 mm Hg) had a 17%-20% higher adjusted HR of death than those with normal pressures ($p < 0.05$). In patients with axial-flow LVADs, elevated systolic BP but not MAP correlated with an increased incidence of stroke (HR, 1.07; 95% CI, 1.03–1.11) per 10 mm Hg increase in systolic BP ($P = 0.001$). Of note, patients in the low MAP and Doppler groups were also more likely to have increased incident RV failure ($p < 0.001$). Authors suggest that overaggressive pharmaceutical management of BP in patients with LVADs should be avoided because excessive afterload reduction may be, in fact, harmful. In general, MAP between 75 and 90 mm Hg seems to be optimal, while deviations in either direction are associated with less favorable outcomes (14).

When arterial line BP and Doppler opening pressure were measured simultaneously, Doppler opening pressure had a good correlation with invasive MAP ($r = 0.742$, $P < 0.0001$) and more closely approximated MAP than systolic BP. Therefore, Doppler opening pressure might be an acceptable, standard non-invasive method of BP measurement (15).



Optimization of Hemodynamics

The importance of achievement and maintenance of optimal hemodynamics in patients with LVAD has gained more and more recognition. In last year's review, we cited a paper by Imamura et al. that demonstrated a decreased rate of all adverse events in LVAD patients if hemodynamics were normal or near normal (16). There are two ways to improve hemodynamics in LVADs: 1) adjust pump parameters and/or 2) maximize the performance of the native left ventricle (LV) by using guideline-recommended heart failure (HF) drugs. The following details the new developments of 2019:

1) Ramp test

The same group of authors (Imamura et al) (17) published a 2019 study (seemingly with some overlap with the previous paper) where LVAD speed was optimized using a ramp test, targeting the following goals: central venous pressure, < 12 mm Hg; pulmonary capillary wedge pressure, < 18 mm Hg; and cardiac index > 2.2 L/min/m². The total hospital readmission rate was lower in the optimized group compared with the non-optimized group (1.15 versus 2.86 events/year, $p < 0.001$). This result was predominantly because of a reduction in the HF readmission rate in the optimized group (0.08 versus 0.71 events/year, $p = 0.016$). Survival was similar. In 39% of patients, hemodynamics could not be optimized. This was most frequently due to a lower pulmonary artery pulsatility index, inability to decrease central venous pressure to normal levels, or because of coexisting atrial fibrillation (17).

Curiously, a novel method of estimation of central venous pressure in patients with LVADs and biventricular pacemakers was suggested by Imamura et al. (18). The empiric formula below had a significant correlation ($r = 0.795$) and good agreement with the measured central venous pressure (mean difference -0.14 ± 1.77 mm Hg). Applying the above equation to the validation cohort showed a strong association with measured central venous pressure ($r = 0.705$).

Central venous pressure = $47.90 - (0.086 \times \text{right atrial lead impedance}) + (0.013 \times \text{RV lead impedance}) - (0.020 \times \text{LV lead impedance})$ (18).

2) Medical management

There is a growing recognition of the need to continue guideline-recommended HF medications after LVAD implantation. Last year, we referenced the lower mortality found when patients maintained HF medications (19). In 2019, Mccolough et al. (20) showed similar results from a new analysis of the INTERMACS database. The overall utilization of this therapy was low. At the 6-months post-LVAD implantation, only 16.2% of patients were receiving triple therapy, and only 22.6% were receiving an angiotensin converting enzyme inhibitor or angiotensin receptor blocker (ACEI/ARBs) and a beta-blocker. The unadjusted 4-year survival estimate for patients receiving neurohormonal blockers was 56.0% (95% CI, 54.5%-57.5%), compared with 43.9% (95% CI, 40.5%-47.7%) for patients not receiving them ($p < 0.001$). Also, patients receiving triple therapy with an ACEI/ARB, a beta-blocker, and an aldosterone antagonist at 6-months



post-LVAD had the longest survival estimate at four years (66.4%; 95% CI, 63.1%-70.0%). In an adjusted model, however, survival benefit became insignificant. The six-minute walk results were also better in the patient cohort on HF medications (20). Another study summarized experiences from two centers, and their data showed treatment with ACEI/ARBs was an independent factor associated with decreased post-LVAD mortality (21).

2019 also yielded the first report on the tolerability of sacibutril/valsartan in patients with LVADs (22). Out of five patients who started taking this medication, three had to discontinue this drug due to hypotension-related symptoms (22).

The favorable effect of LVAD on diabetes has been previously reported (23-26); however, for the first time last year, we demonstrated a significant reduction in fasting blood glucose after LVAD implantation in both diabetic and non-diabetic patients (27). In diabetic patients, there was an overall reduction in insulin requirements from an average of 29.2 units per day before the LVAD to 16.2 units per day before discharge ($p = 0.038$) (27). In addition, the beneficial effect of an LVAD on other metabolic and hormonal variables, such as free and total testosterone, thyroid-stimulating hormone, and free T4, was shown by Nguen et al. (28). Before implantation, 75% of patients had insulin resistance, 86% of men and 39% of women had low free testosterone, and 44% of patients had abnormal thyroid function. There was a significant improvement in all of the measures following implantation ($p < 0.001$ for all). Patients with a normal hemoglobin A1C ($< 5.7\%$) following implantation also had a higher 1-year survival free of HF readmissions (78% versus 23%; $P < 0.001$). Patients with metabolic parameters within normal range following LVAD implantation also had higher 1-year survival free of HF readmissions (92% versus 54%; $p = 0.04$).

Radiation Therapy in LVAD

A case of radiation therapy for lung cancer in a patient with a HM3 device was reported in 2019, and radiotherapy appeared to be safe in terms of continued LVAD function (29). In the past, there were eight case reports on radiation therapy with LVADs (HMII and Heartware) in the radiation field (29). The maximal reported doses received directly to a VAD was 4900 cGy with a mean of 1922 cGy for a gastroesophageal junction tumor. None of the patients experienced LVAD-related complications or pump malfunction (29).

Recovery Evaluation

Last year, we published the flow chart for recovery evaluation (30), based on the work of the Berlin group (31). This year, Nir Uriel's group at the University of Chicago shared their reverse ramp test protocols (Table 1), which assess myocardial recovery (32). The group routinely performs such tests at the 6–12 months post-LVAD implantation timepoints in patients < 50 years of age with a short duration of HF (< 2 –5 years). In the reverse ramp test, device speed is reduced to minimal settings, which requires anticoagulation with an international normalized ratio (INR) of 2–3.5 to limit the risk of device thrombosis.



Interestingly, with progressive decreases in LVAD speed, and hence reloading of the LV, the left ventricular ejection fraction improved from baseline post-VAD ($30.67\% \pm 10.15\%$) to the last step ($46.05\% \pm 14.19\%$). The pulmonary capillary wedge pressure also increased from 8.86 ± 3.08 mm Hg to 12.50 ± 2.04 mm Hg; the mean pulmonary artery pressure remained stable; and the central venous pressure increased minimally from 7.14 ± 2.91 mm Hg to 8.17 ± 3.34 mm Hg. Cardiac output decreased slightly during the test from 5.92 ± 0.55 L/min to 5.44 ± 0.51 L/min. As a result, three out of seven patients were suitable for pump decommissioning (32).

Table 1. Reverse ramp protocol for different pumps

	Initial speed, rpms	Rpm decrease per step	Time between steps, minutes	Final speed, rpms
HeartWare	2,400	199	3	1,800
HMII	8,000	400	3	6,000
HM3	5,000	100	3	4,000
Echo parameters recorded for each step	left ventricular end-diastolic diameter, left ventricular end-systolic diameter, aortic valve opening, degree of aortic insufficiency, and mitral regurgitation			
Hemodynamic parameters recorded for each step	central venous pressure; systolic, diastolic and mean pulmonary artery pressure; pulmonary capillary wedge pressure; pulmonary artery saturation; cardiac output; cardiac index			
Pump parameters recorded for each step	HM II and HM3: speed, pulsatility index, flow, power Heartware: speed, upper flow, lower flow, average flow, power			

Rpms – revolutions per minute; HMII – HeartMate II; HM3- HeartMate 3

LVAD and Valves

Mitral Valve

MitraClip (Abbott) is becoming an established procedure in many programs. So far, LVADs have been implanted in patients with MitraClips, and reports indicate the procedure is safe. Current data indicates that there is no need for additional procedures on the mitral valve (33).

Aortic Valve

New data were published about the importance of aortic regurgitation in LVADs. If the regurgitant fraction exceeds 30%, one-year survival free of major adverse



events (bleeding, stroke, pump thrombosis) was 44% compared to 67% in patients without significant aortic insufficiency ($P = 0.018$) (34).

Transcatheter aortic valve replacement was again found to be a feasible and safe procedure in LVAD patients, resulting in complete resolution of aortic regurgitation (35).

Tricuspid valve

The topic of concomitant procedures on the tricuspid valve during LVAD implantation remains controversial. By some data, such procedures did not improve patient outcomes but reduced the incidence of 30-day readmission (36). Other data indicates the concomitant procedure increased cardiac output with unknown clinical consequences (37).

Arrhythmia

There was an important analysis of the site of origin of ventricular tachycardia in LVADs (38). Scar-related re-entry was the predominant mechanism (90.3%), and cannula-related ventricular tachycardia was found only in 19.3% cases. In cases of electrical storm, ablation was successful in 90% of the cases (38).

Ventricular arrhythmia continues to be an indicator of increased mortality after LVAD. When ventricular arrhythmia occurs in the first month after LVAD implantation, especially if presenting as electrical storm, it was associated with a 7-fold increase of 30-day mortality (39). Fortunately, after the patients are discharged alive, early ventricular arrhythmias have no further bearing on the prognosis (39). Congruently, in another study, 32.8% of patients presenting with electrical storm died within the next two weeks (40). Electrical storm was defined as at least three separate episodes of sustained ventricular tachycardia or appropriate implantable cardioverter defibrillator (ICD) shocks within a 24-hour period (40).

Two new observational studies from Cleveland Clinic analyzed the presence of ICDs (41) and atrial fibrillation/flutter (42) in LVAD patients. Neither was associated with different outcomes than in patients without ICDs or atrial tachyarrhythmia, respectively. There do not seem to be strong data in favor of implanting ICDs in patients who did not have them before the LVAD (41). Also, there is no evidence that controlling the rate in atrial arrhythmias improves outcomes. Atrial fibrillation or flutter was not associated with increased mortality, thromboembolism, or bleeding (38, 42).

Also, this year, a scientific statement from the American Heart Association was published. It provides detailed recommendations on the management of arrhythmias in LVAD recipients (43).

Complications of the VADs

LVAD Outflow graft obstruction

Last year, we dedicated a significant portion of the review to outflow graft obstruction research. The following summarizes the findings:

- Surgical Technique: Gore-tex around the outflow tract



- Timing: Months to years after the implantation
- Symptoms: HF, low flows, with or without low flow alarm, and decreased pulsatility index
- Hemolysis: No
- Diagnosis: Computer tomography angiography (CTA)
- Treatment: Stenting
- Prevention: Discontinuation of wrapping the outflow tract with the Gore-tex (30)

However, despite several published cases and case series, the incidence of this complication remains unknown. In a 2019 retrospective study, all patients with CTAs done for any reason were examined for the outflow graft narrowing, defined as the internal luminal diameter of the outflow graft < 10 mm (44). 14% of patients had evidence of outflow graft lumen narrowing, all in HeartMate® devices and all within the portion covered by the bend relief, with biodebris between the bend relief and the outflow graft. Time from implant to scan ($p < 0.001$), nonischemic cardiomyopathy ($p = 0.017$), and patient age at the device implant ($p = 0.003$) were significantly associated with LVAD outflow graft narrowing (44).

Because patients had a CTA for clinical reasons, one of which is suspected pump thrombosis or low flow state, this incidence rate may be higher than in all LVAD recipients. Curiously, in this series, there were no cases of outflow graft obstruction in HeartWare® devices. Authors postulate that the HeartWare design allows greater accumulation of debris without lumen narrowing (44). However, last year, we summarized published case reports, which included four cases of outflow graft obstruction in HeartWare pumps. This year, Nathan et al. published the largest case series of 12 outflow graft obstruction cases (45). 25% (3/12) cases occurred with the HeartWare device. Another series of note included five patients (46); four of these cases had HeartWare devices.

Stroke

Since the Evaluate the HeartWare Ventricular Assist System for Destination Therapy of Advanced Heart Failure (ENDURANCE) Trial was published in 2017 (47), the increased rate of strokes on HeartWare devices as compared to HMII support (29.7% vs. 12.1%, $P < 0.001$) has been heeded by many as a word of caution when it comes to the choice of pump.

However, in 2019, Li et al. identified and analyzed neurologic events in key clinical trials and registries (48). He compared the HMII, HM3, and HeartWare devices and found the neurologic event rates were comparable when standardized as events per patient-year (HM3 = 0.17-0.21; HMII = 0.19-0.26; HeartWare = 0.16-0.28) (48). It appears that patient selection was key to the earlier reported discrepancies, and no pump outperforms others in terms of stroke rate.

Gastrointestinal Bleeding

Gastrointestinal bleeding on LVAD support is a frustrating complication requiring extensive work up in search of a bleeding cause and location. Axelrad et al. proposed an algorithm for LVAD-associated GIB (49). Adherence to this algorithm was associated with a 68% increase in the diagnostic yield and a 113% increase in the therapeutic yield of endoscopy. Also, it decreased the length of stay by four



days and reduced the number of procedures per patient by 27% and cost by 18% (Figure 4).

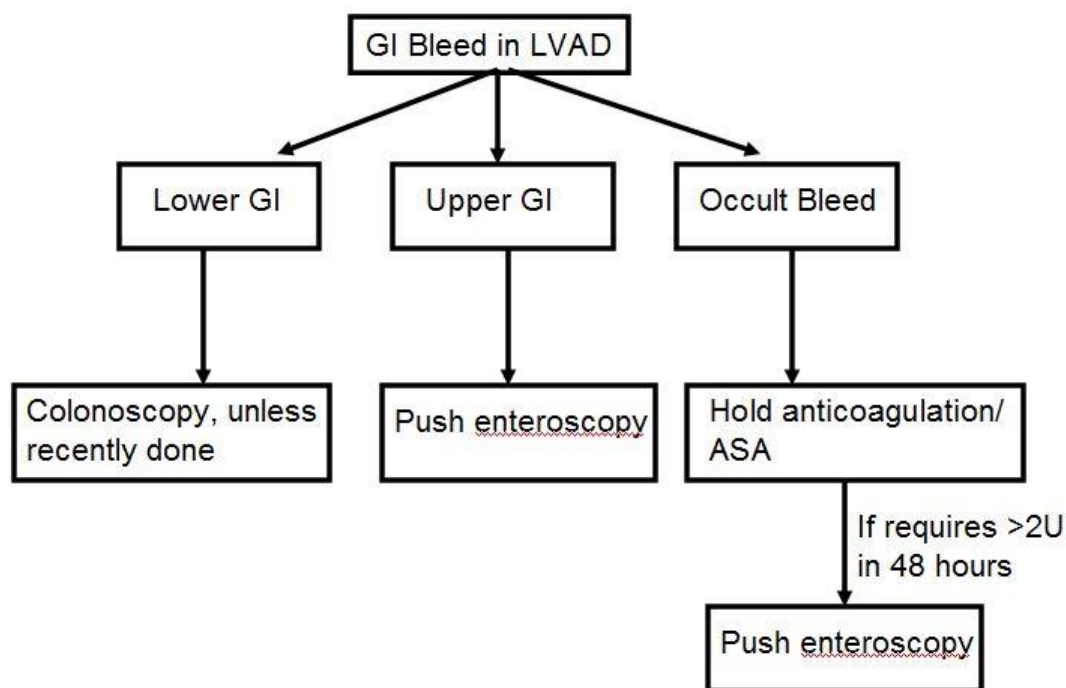


Figure 4. Algorithm for diagnostic workup for gastrointestinal bleeding. Modified from Axelrod et al. (49)

In terms of treatment, there is growing evidence that the medical management of patients on LVAD may produce benefits seemingly unrelated to HF, BP control, or LV reverse remodeling. In the retrospective cohort from the University of Minnesota, ACEI/ARB use was associated with a reduction in the incidence rate of GIB (unadjusted 78% reduction; 95% CI, 0.10-0.48; $p < 0.00001$; adjusted 67% reduction; 95% CI, 0.15-0.71; $p = 0.005$) (50). This protective effect is similar to the observations of Houston et al. (51).

Another new study also showed that patients who received an ACEI/ARBs within 30 days after LVAD implantation had a 57% reduction in the risk of major GIB, defined as bleeding requiring ≥ 2 units of packed red blood cells or resulting in death (HR, 0.43; 95% CI, 0.19-0.97; $p = 0.042$) and a 63% reduction in the risk of arterio-venous malformations-related GIB. Moreover, when the mean daily lisinopril-equivalent ACEI /ARB dose was >5 mg, the risk of major GIB decreased in a dose-threshold manner (HR, 0.28; 95% CI, 0.09-0.85; $p = 0.025$). Prevention of the development of arterio-venous malformations was proposed as a potential mechanism (52).



Other medications may also play a role in GIB. A retrospective review found that selective serotonin reuptake inhibitors, commonly prescribed for depression, are associated with GIB post-LVAD (53). Patients receiving these medications developed GIB due to arterio-venous malformations at the rate of 24.8% versus 14.7% in patients not receiving them (53).

Thalidomide therapy was again found to be effective for GIB in LVAD patients, reducing the risk of rebleeding (HR, 0.23; $p = 0.022$). The median number of GI bleeds per year was reduced from 4.6 to 0.4 ($p = 0.0008$), and the packed red blood cell requirement was lower (36.1 vs. 0.9 units per year, $p = 0.004$) in those on thalidomide therapy. The adverse event rate with thalidomide was high at 59%, with symptoms resolution in most following dose reduction without increased bleeding (54).

RV failure

An interesting case was reported from the University of Toronto, where a patient with an LVAD and RV failure progressed to asystole with a complete cardiac standstill (55). Her hemodynamics were maintained by LVAD with no contribution from the RV until she received a heart transplant (55). In an equally interesting commentary, Imamura (56) compared this case with the one a patient on LVAD support and sustained ventricular fibrillation. He suggested that in such cases of "Fontan-like circulation," with LVAD performing the function of the LV and RV being completely passive, circulation can be maintained with the following hemodynamic parameters: central venous pressure of 15–20 mm Hg, pulmonary capillary wedge pressure of 10–15 mm Hg, and low PVR around 2.0 Wood units (56). An elevated central venous pressure was needed because a relatively high-volume status is required to maintain the preload of LV without any help from the RV.

What is new in VA ECMO World?

The 2019 American Heart Association Focused Update on Advanced Cardiovascular Life Support confirmed that there is insufficient evidence to recommend the routine use of extracorporeal cardiopulmonary resuscitation (ECPR) for patients with cardiac arrest (57). ECPR may be considered for selected patients as rescue therapy when conventional CPR efforts are failing in settings in which it can be expeditiously implemented and supported by skilled providers (Class 2b; Level of Evidence C-LD) (57).

Like in continuous-flow LVADs, blood management on VA ECMO remains a topic of discussion. While lower pressure can lead to end-organ hypoperfusion, a higher pressure may compete with ECMO flow and cardiac output. In a retrospective study of 124 patients, the average MAP was significantly higher in patients who survived to discharge (82 ± 5.6 vs. 78 ± 5.5 mm Hg, $p = 0.0003$) (58). Survival was best with a MAP higher than 90 mm Hg (71%) and worst with a MAP less than 70 mm Hg, where no patient survived. MAP was an independent predictor of survival to discharge by multivariate analysis (odds ratio 1.17, $p = 0.013$). Also, patients with a higher MAP had a lower incidence of kidney injury ($p = 0.007$) (58).

For the first time, the excessive fluid accumulation while on VA ECMO support was directly linked to increased short-term mortality (59). The net fluid balance was



higher in non-survivors than in survivors on Day 1 ECMO support (47.3 [18.1-71.9] vs 19.3 [1.5-36.2] mL/kg, $p < 0.0001$) and Day 2 (30.6 [14.8-71.0] vs 10.1 [-9.8-34.7] mL/kg, $p=0.025$), as was the cumulative fluid-balance over the first 5 days (107.3 [40.5-146.2] vs 53.0 [7.5-74.3] mL/kg, $p= 0.04$). Moreover, a threshold of 38.8 mL/kg predicted mortality with a sensitivity of 60% and specificity of 83% (59).

Another topic of growing interest is LV venting. A systematic literature review analyzed mortality on VA ECMO based on the timing of LV venting (60). Overall, LV venting significantly improved weaning from VA ECMO (odds ratio, 0.62; 95% CI, 0.47-0.83; $p= 0.001$) and reduced 30-day mortality (risk ratio 0.86; 95% CI, 0.77-0.96; $p= 0.008$) but not in-hospital or 6-month mortality. Importantly, early (< 12 hours) but not late (≥ 12 hours) LV venting reduced short-term mortality significantly. In terms of the method of venting, the majority of patients had an intra-aortic balloon pump (43%) (60).

Another analysis of published literature found that the intra-aortic balloon pump was chosen as a venting device in 91.7% of patients on VA ECMO who had LV venting (61). Mortality was lower in patients with (54%) versus without (65%) LV unloading while on VA-ECMO (risk ratio, 0.79; 95% CI, 0.72-0.87; $p < 0.00001$) (61).

Along the same lines, Vallabhassula et al. (62) reviewed the literature to compare early mortality in patients with cardiogenic shock treated with ECMO plus Impella (Abiomed) (ECPELLA) to VA ECMO alone. They found that the use of ECPELLA was associated with higher weaning from VA ECMO and bridging to permanent LVAD or cardiac transplant. Also, the studies that accounted for differences in baseline characteristics between treatment groups reported lower 30-day mortality with ECPELLA versus VA ECMO (62).

LV venting with a transseptal 24-Fr multiple-side-hole cannula with a length of > 55 cm that could effectively decompress both the right and left heart was reported by Na et al. (63). If the device was used prophylactically, before LV distension, the 30-day mortality rate was 5.6%, but if the cannula was inserted for treatment of LV distension after it occurred, the mortality was 34.4% ($P= 0.036$). The rate of successful weaning from ECMO and the duration of ECMO support were not significantly different between the groups. However, the rate of bridging to cardiac replacement therapy, such as heart transplantation or LVAD, was significantly higher in the prophylactic group (66.7%) than in the therapeutic group (37.5%) ($P= 0.048$) (63).



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